UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

March 3, 2008

MEMORANDUM

Subject: Acute Toxicity Review for EPA Reg. No. 10324-56
DP Barcode 347425

From: Wallace Powell, Biologist
Chemistry and Toxicology Team
Product Science Branch
Antimicrobials Division (7510P)

Through: Karen Hicks, Team Leader
Chemistry and Toxicology Team
Product Science Branch
Antimicrobials Division (7510P)

Michele E. Wingfield, Chief
Product Science Branch
Antimicrobials Division (7510P)

To: Velma Noble, PM 31/ Tracy Lantz
Regulatory Management Branch I
Antimicrobials Division (7510P)

Applicant: Mason Chemical Company

ACTIVE INGREDIENT	% by wt.
(Code 069104) Alkyl* dimethyl benzyl ammonium chloride *(60%C14, 30%C16, 5%C18, 5%C12)	6.25
(Code 069154) Alkyl* dimethyl ethylbenzyl ammonium chloride *(68%C12, 32%C14)	6.25

BACKGROUND

In support of a label amendment for the subject product MAQUAT 256, EPA Registration No. 10324-56, the applicant has submitted studies for acute oral toxicity, acute dermal toxicity, skin

irritation, and skin sensitization. Reviews of the studies are attached to this memorandum. A waiver request for eye irritation data was also submitted (MRID 472874-08).

Changes to the human-hazard precautionary statements in the proposed label versus the last EPA-accepted label (accepted 8/16/2005) are limited to wording that reflects less skin irritation hazard. There are no changes to the first-aid statements. Also, apparently no new formulation is being proposed.

Accordingly, new acute toxicity studies other than skin irritation data were not necessary to support the proposed registration amendment. However, Product Science Branch (PSB) offers the following comments.

RECOMMENDATION

The submitted **acute oral toxicity** study is classified as Acceptable, Non-Guideline. As such, the study can be considered useful in support of the subject registration for the time being but cannot be cited later (e.g., for reregistration or for another product or by another registrant). The test method used – traditional method corresponding to OECD Guideline 401 – is not a current Guideline method. (The current methods are indicated in the current, December 2002, 870.1100 acute oral toxicity guidance document, which can be found at *http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Revised.*)

The submitted **acute dermal toxicity** study is acceptable.

For **acute inhalation toxicity**, the Cite-all method of support has been proposed. This is acceptable. Although the applicant did not reference a similar registered product, PSB is aware that MAQUAT 256 is substantially similar to EPA Reg. No. 10324-164. Reg. No. 10324-164 is labeled according to Category III for acute inhalation toxicity.

The **eye irritation** waiver request is acceptable based on the results of the submitted skin irritation study.

The submitted **skin irritation** study is acceptable.

The submitted **skin sensitization** study is unacceptable but potentially upgradable:

1. For the main study, no data was reported for the induction phase. For each induction exposure, graded reactions should be reported for each animal in order to confirm the adequacy of the induction concentration. (The reported results of the irritation screen are helpful in this regard but in PSB's opinion are insufficient.)
2. For the positive control study, data for the naïve control group was not reported. Reactions for each animal should be reported.
3. For the positive control study, the number of animals in the naïve control group was not reported.

Acute toxicity profile

The acute toxicity profile, as based on the newly submitted data support only, is as follows:

Study	MRID	Toxicity Category	Status
Acute Oral Toxicity	472874-05	III	Acceptable, Non-Guideline
Acute Dermal Toxicity	472874-06	III	Acceptable
Acute Inhalation Toxicity	Cite-all	III	Acceptable
Primary Eye Irritation	Waiver request	I	Waived
Primary Skin Irritation	472874-07	I	Acceptable
Dermal Sensitization	472874-09	---	Unacceptable

Product labeling

The First Aid statements in the proposed label (which is dated by registrant 11/19/2007) are acceptable.

The two proposed changes to the human-hazard precautionary wording are unacceptable. (They are "Causes skin irritation" and "Avoid contact with skin.")

As per the Agency's *Label Review Manual*, the following human-hazard precautionary statements are indicated for this product:

> DANGER. Corrosive. Causes skin burns and irreversible eye damage. Harmful if swallowed, inhaled, or absorbed through skin. Do not get in eyes, on skin, or on clothing. Avoid breathing vapor or spray mist. Wear [*specify appropriate protective eyewear such as goggles, face shield, or safety glasses*]. Wear [*specify appropriate protective clothing and gloves*]. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco or using the toilet. Remove and wash contaminated clothing before reuse.

If the products gets classified later as a dermal sensitizer, then a statement such as, "Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals," will also be required.

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (OPPTS 870.1100)

Product Manager: 31
MRID No.: 472874-05

Reviewer: W. Powell
Study Completion Date: April 26, 2005
Report No.: 05-014-3

Testing Laboratory: Tox Monitor Laboratories, Inc., Oak Park, IL
Author: Michael Kukulinski

Quality Assurance (40 CFR §160.12): A Quality Assurance (QA) statement was included. A statement of Good Laboratory Practice (GLP) compliance was included stating that this study was conducted in accordance with U.S. EPA GLP Standards, 40 CFR 160.

Test Material: Maquat 256, a clear liquid
Batch #: 1621-69

Dosage: 5.0, 2.5, 1.25, and 0.625 g/kg

Species: Rat, Sprague-Dawley derived, albino
Sex: 5 Males, 5 Females per dose level. Females were nulliparous and non-pregnant.
Age: Young adult (6-10 weeks old)
Weight: 200-298 grams
Source: Harlan Sprague Dawley – Indianapolis, IN
Housing: Temperature Range: 64-79 °F (i.e., approx. 17.8-26.1°C)
Humidity Range: 30-70%
Photoperiod: Not reported
Acclimation: At least 5 days

Conclusion:

1. **LD_{50} (mg/kg)**: 1,890 mg/kg Combined (males and females)
(95% confidence interval of 1,500-2,390 mg/kg)

2. **Toxicity Category**: III (Note: a calculated LD_{50} for each sex individually would also be well within this toxicity category)

3. **Classification**: Acceptable, Non-Guideline (see first *Deviation* below)

Procedure/Reporting Deviations from Guideline 870.1100:

- The test method used – traditional method corresponding to OECD Guideline 401 – is not a current Guideline method.
- The guidelines state that animals should be between 8 and 12 weeks old at commencement of dosing. The animals used in this study were between 6 and 10 weeks old.
- The light/dark cycle of the animal room was not reported (though the report states that it was controlled).

Results:

Overall mortality at the 5 g/kg dose level was 100% by Day 5; at the 2.5 g/kg dose level, 80% by Day 2; and at the 1.25 g/kg dose level, 10% by Day 2.

Reported Mortality

Dosage (g/kg)	Number Deaths / Number Tested		
	Male	Female	Total
5.0	5 / 5	5 / 5	10 / 10
2.5	5 / 5	3 / 5	8 / 10
1.25	1 / 5	0 / 5	1 / 10
0.625	0 / 5	0 / 5	0 / 10

Clinical signs observed during the observation period included hypoactivity, loose stool, piloerection, and hunched posture. Clinical signs in the 0.625 g/kg dose group were unremarkable.

All surviving test animals gained body weight during the 14-day observation period.

Gross necropsy findings were limited to animals that died during the observation period. Findings were limited to the gastrointestinal system and a mottled appearance of the liver. Findings were almost entirely limited to the 5.0 and 2.5 g/kg dose groups.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (OPPTS 870.1200)

Product Manager: 31
MRID No.: 472874-06

Reviewer: W. Powell
Study Completion Date: April 5, 2005
Report No.: 05-014-4

Testing Laboratory: Tox Monitor Laboratories, Inc., Oak Park, IL
Author: Michael Kukulinski

Quality Assurance (40 CFR §160.12): A Quality Assurance (QA) statement was included. A statement of Good Laboratory Practice (GLP) compliance was included stating that this study was conducted in accordance with U.S. EPA GLP Standards, 40 CFR 160.

Test Material: Maquat 256, a clear liquid
Batch #: 1621-69

Dosage: 2.0 g/kg

Species: Rabbit, New Zealand albino
Sex: 5 Males, 5 Females
Females were nulliparous and non-pregnant.
Age: Young adult, at least 12 weeks
Weight: 2.01-2.35 kg
Source: Kuiper Rabbitry – Gary, IN
Housing: Temperature: 61-72 °F
Humidity: 30-70%
Photoperiod: Not reported
Acclimation: At least 5 days

Summary:

1. **Estimated acute dermal LD_{50}** for male and female rabbits was greater than 2,000 mg/kg.
2. **Toxicity Category**: III
3. **Classification**: Acceptable

Procedure/Reporting Deviations from Guideline 870.1200:

- The light/dark cycle of the animal room was not reported (though the report states that it was controlled).

Results:

Administration of the test substance by dermal application at a dose of 2.0 g per kg body weight to male and female rabbits produced no mortality during the 14 day observation period. The results indicate that the dermal LD_{50} of the sample was greater than 2.0 g/kg.

Reported Mortality

Dose Level (g/kg)	Number Dead / Number Tested		
	Males	Females	Total
2.0	0 / 5	0 / 5	0 / 10

Clinical signs included erythema, edema, and eschar at the test article application site in all ten test animals. Eschar was observed in all ten animals at the application site on Days 5 through 14. Necrosis was observed at the application site in six of ten animals on Days 8 through 14.

Internal necropsy findings were unremarkable. External necropsy findings were limited to necrosis, eschar, or discoloration, at the test article application site.

Five of the ten animals (four males and one female) lost weight during the study.

DATA REVIEW FOR ACUTE DERMAL IRRITATION TESTING (OPPTS 870.2500)

Product Manager: 31
MRID No.: 472874-07

Reviewer: W. Powell
Study Completion Date: November 17, 2005
Report No.: 05-014-2

Testing Laboratory: Tox Monitor Laboratories, Inc., Oak Park, IL
Author: Michael Kukulinski

Quality Assurance (40 CFR §160.12): A Quality Assurance (QA) statement was included. A statement of Good Laboratory Practice (GLP) compliance was included stating that this study was conducted in accordance with U.S. EPA GLP Standards, 40 CFR 160.

Test Material: Maquat 256, a clear liquid
Batch #: 1621-69

Dosage: 0.5 mL

Species: Rabbit, New Zealand White
Sex: 6 Females. Nulliparous and non-pregnant.
Age: 8-10 weeks
Weight: 2.09-2.35 kg
Source: Kuiper Rabbitry, Gary, IN
Housing: Temperature: 61-72°F (i.e., approx. 16.1-22.2°C)
Humidity: 30-70%
Photoperiod: Not reported
Acclimation: At least 5 days

Summary:

1. **Toxicity Category**: I
2. **Classification**: Acceptable

Procedure/Reporting Deviations from Guideline 870.2500:

- The guidelines state that irritation responses should be scored with 30-60 minutes after patch removal. The first reading reported by the laboratory for each animal was at 4.5 hours after patch removal.
- The light/dark cycle of the animal room was not reported (though the report states the light was controlled).

Results:

Degree of observed erythema reached as high as moderate to severe (grade 3 on the Draize scale), in 4 of 6 animals at 72 hours and 168 hours (7 days); and severe (grade 4) in 1 of 6 animals at 24, 72, and 168 hours. Edema was observed as severe (grade 4 on the Draize scale) in 2 of 6 animals at 24 hours, and as moderate (grade 3) in 2 of 6 animals at 48 hours and in 1 of 6 animals at 72 hours. Edema cleared completely by the end of the observation period.

Coriaceousness/eschar was reported in all 6 animals at 168 hours, in 5 of 6 animals at 336 hours (14 days), and in 3 of 6 at 504 hours (21 days).

Under the conditions of this study, Maquat 256 is classified as severely irritating to the skin.

Individual Skin Irritation Scores

Animal No.	Sex	Erythema / Edema						
		Time After Patch Removal						
		4.5 hrs	24 hrs	48 hrs	72 hrs	168 hrs	336 hrs	504 hrs
704	F	2 / 2	2 / 4	3 / 3	4 / 2	4 / 1	3 / 0	1 / 0
705	F	2 / 2	2 / 3	2 / 2	3 / 2	3 / 2	3 / 0	3 / 0
706	F	2 / 1	2 / 2	3 / 2	3 / 3	3 / 2	3 / 0	2 / 0
707	F	2 / 2	2 / 2	3 / 2	3 / 2	3 / 2	3 / 1	3 / 0
708	F	2 / 2	2 / 4	3 / 3	3 / 2	3 / 2	3 / 1	3 / 0
709	F	2 / 1	2 / 2	2 / 2	2 / 1	2 / 1	2 / 0	1 / 0

DATA REVIEW FOR SKIN SENSITIZATION TESTING (OPPTS 870.2600)

Product Manager: 31
MRID No.: 472874-09

Reviewer: W. Powell
Study Completion Date: April 29, 2005
Report No.: 05-014-5

Testing Laboratory: Tox Monitor Laboratories, Inc. – Oak Park, IL
Author: Michael Kukulinski

Quality Assurance (40 CFR §160.12): A Quality Assurance statement was included. A statement of Good Laboratory Practice (GLP) compliance was included stating that the study was conducted in accordance with U.S. EPA GLP Standards, 40 CFR 160.

Test Material: Maquat 256, a clear liquid
Batch #: 1621-69
0.4 mL applied 7.5% w/w in distilled water for induction,
3.5% w/w in distilled water for challenge

Historical Positive Control:

Substance: 1-Chloro-2,4-dinitrobenzene
Applied 0.1% in 80% aqueous ethanol for induction, 0.1% in acetone for challenge

Study date: 12/21/2004

Animals: 10 guinea pigs, albino; young adult (200-500 g range).
Naïve control group: Number of animals not reported.

Test Group Animals:

Species: Guinea pig, Hartley
Pilot/Screen: 2 (1 Male, 1 Female)
Test Group: 20 (10 Males, 10 Females)
Naïve Control: 10 (5 Males, 5 Females)
Age: Young adult
Weight: 300-500 grams (initial)
Source: Kuiper Rabbitry – Gary, IN
Housing: Temperature Range: 64-79°F
Relative Humidity: 30-70%
Photoperiod: 12-hour light/dark cycle

Acclimation: At least 5 days

Method: Buehler

Summary:

1. Maquat 256 did not appear to be a contact sensitizer.
2. **Classification**: Unacceptable, based on the first three *Deviations* listed below.

Procedure/Reporting Deviations from Guideline 870.2600:

1. For the main study, no data was reported for the induction phase. For each induction exposure, graded reactions should be reported for each animal in order to confirm the adequacy of the induction concentration. (The reported results of the irritation screen are helpful in this regard but in PSB's opinion are insufficient.)
2. For the positive control study, data for the naïve control group was not reported. Reactions for each animal should be reported.
3. For the positive control study, the number of animals in the naïve control group was not reported.
4. For the positive control study, the procedure and the dose concentrations and amounts were not reported in the study report proper. However, they were given in the *Protocol*.

Because all Deviations are reporting deficiencies, the study is potentially upgradable.

Results:

In the Test Group study, based on comparable challenge response between the test group and naïve control group, study results suggests that Maquat 256 was not a contact sensitizer. Results of the historical Positive Control study suggest that a positive response was achieved, but naïve control data was not reported.

Skin Reaction Scores

	Induction						Challenge	
	1		2		3			
Concentration	7.5%		7.5%		7.5%		3.5%	
Hours[1]	24	48	24	48	24	48	24	48
Animal No. / Sex								
Test Group								
95 / M	*	*	*	*	*	*	0	0
96 / M	*	*	*	*	*	*	0	0
97 / M	*	*	*	*	*	*	0	0
98 / M	*	*	*	*	*	*	0	0
99 / M	*	*	*	*	*	*	0	0
100 / M	*	*	*	*	*	*	0	0
101 / M	*	*	*	*	*	*	0	0
102 / M	*	*	*	*	*	*	0.5	0
103 / M	*	*	*	*	*	*	0	0
104 / M	*	*	*	*	*	*	0	0
105 / F	*	*	*	*	*	*	0	0
106 / F	*	*	*	*	*	*	0.5	0
107 / F	*	*	*	*	*	*	0	0
108 / F	*	*	*	*	*	*	0	0
109 / F	*	*	*	*	*	*	0	0
110 / F	*	*	*	*	*	*	0	0
111 / F	*	*	*	*	*	*	0	0
112 / F	*	*	*	*	*	*	0	0
113 / F	*	*	*	*	*	*	0	0
114 / F	*	*	*	*	*	*	0	0
Naïve Control Group								
115 / M	---	---	---	---	---	---	0.5	0
116 / M	---	---	---	---	---	---	0	0
117 / M	---	---	---	---	---	---	0	0
118 / M	---	---	---	---	---	---	0.5	0
119 / M	---	---	---	---	---	---	0	0
120 / F	---	---	---	---	---	---	0	0
121 / F	---	---	---	---	---	---	0	0
122 / F	---	---	---	---	---	---	0	0
123 / F	---	---	---	---	---	---	0	0
124 / F	---	---	---	---	---	---	0	0

[1] Hours after induction dose.
*Not reported.